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Title: Implant material and method for the manufacture thereof

Applicant: Bioapatite AB

The present invention relates to a biocompatible implant material for restoring bone tissue in human or animal bodies and to a method of preparing such material as well as a method for restoring bone tissue in human or animal bodies.

The implantation of materials of different types in the human or animal body in order to replace bone portions which have been worn out or which have deteriorated due to diseases or of other reasons, is steadily increasing. Suitable materials used for said purpose are titanium and minerals and ceramics such as high-purity alumina, tricalcium phosphate and calcium aluminate, and preferred materials are materials having the same chemical composition and crystal structure as those materials that are built up by the living organism, such as calcium hydroxyapatite and fragments of natural bone. In order to eliminate the risk of immunological diseases, synthetic materials of this type are of increasing interest, and one synthetic material of this type which has come into use for restoring bone tissue is polycrystalline mineral calcium hydroxyapatite and particularly the non-resorbable type thereof which has the formula $Ca_{10}(PO_4)_6(OH)_2$ and which is the main constituent of the bones in the body wherein the organic matrix of the bone tissue is received. Said material serves as a "climb structure" for bone tissue and prevents connective tissues from growing into the region of the bone which has been destroyed and is to be restored. Calcium hydroxyapatite of the abovementioned formula is manufactured by Asahi Optical Co., Ltd., Tokyo, Japan, and is marketed under the trade mark APACERAM. This material is pure calcium hydroxyapatite, substantially corresponding to the mineral substance in bone. The material is available as preformed pieces, such as tooth roots, bones for the middle ear and elements for brain surgery and also as a raw material in the form of blocks, which can be worked by sawing, milling and boring and which are of different shapes and porosities, and as a particulate material in the form of granules, i.e. particles of regular or irregular shapes, the sizes of which are of the orders from 0,1 mm to some millimeters. The blocks are used for large implants, eventually after having been properly shaped, and the granules are used for filling bone cavities as well as in combination with said blocks. Thus, since calcium hydroxyapatite is a hard and brittle material as most ceramics are, it is difficult to impart to the blocks the exact shapes needed for the actual implantations, by cutting or otherwise working the blocks, and therefore said granules are used in combination with the shaped block pieces to fill out gaps or spaces existing between the shaped block pieces and the surrounding intact bone tissue.

In most cases the abovementioned granules or particles are mixed with blood or a physiological saline solution in order to form a mass and to wet the surfaces of the granules or particles to eliminate surface tension phenomena when applying said granules or particles to the bone. A drawback to this technique is that, when the material has been applied to the bone, blood that may come from adjacent bleeding portions of the body or any other secreted body fluid will dilute the particulate mass and may even carry away the material from the site of application.

The object of the present invention is to overcome this drawback such that the material can be easily applied and resist dilution for keeping the material in the place of application.

The object of the invention referred to above is achieved according to a general aspect thereof by providing an implant material for restoring bone tissue, comprising a particulate biocompatible non-organic bone tissue substitute and a mixture of an aqueous liquid and a monoglyceride, which material remains in the liquid phase below a predetermined temperature.

Monoglycerides are unsaturated fatty acids with the ability to change, at a constant temperature, from liquid condition to a gel-like structure of high viscosity only by swelling in water or an aqueous liquid. By mixing the particulate material with a mixture of monoglyceride and water below a predetermined temperature, preferably below body temperature (about 36°C), the particles will, together with the mixture of monoglyceride and water, form a toothpaste-like mass of a relatively low viscosity, which can easily be applied to a bone cavity or to a bone with an implant body mounted therein or thereupon by smearing the mass onto the surface of said bone or the surface of said bone and implant, respectively. The viscosity of the mass will then be temporarily increased due to the increased temperature at the application site, but when the mass comes into contact with body fluid, such as blood or the humidity from soft tissue, it will harden in a few seconds to form a moldable well confined plastic body. This change of the viscosity of the implant material is due to the formation of a cubic liquid crystalline phase when the material is brought into contact with the body fluid or any other liquid present on or supplied to the site of application of the material, said material being a precursor for the formation of the cubic liquid crystalline phase.

In the preferred embodiment of the invention, the non-organic bone tissue substitute is selected from the group consisting of calcium hydroxyapatite, alumina, tricalcium phosphate and calcium aluminate, whereby calcium hydroxyapatite is the preferred material.

The invention also relates to a method of preparing an implant material for restoring bone tissue, said method comprising mixing a particulate biocompatible non-organic bone

tissue substitute with a mixture of an aqueous liquid and a monoglyceride, which material remains in the liquid phase below a predetermined temperature.

Moreover, the present invention provides a method of restoring bone tissue in a bone of a human or animal body, which comprises applying an implant material of low viscosity, consisting of a particulate biocompatible non-organic bone tissue substitute and a mixture of an aqueous liquid and a monoglyceride, which material remains in the liquid phase below a predetermined temperature, and bringing said material into contact with an aqueous liquid for transforming or converting the phase of the material into a cubic liquid phase, whereby the material forms a well confined plastic mass of high viscosity. The application can be carried through by using a conventional one-way syringe, the low viscosity implant material being received by the syringe and being ejected therefrom to the region of the bone where the mass is to be applied.

The applied material may after conversion of its phase to the cubic liquid phase be given its final form at the application site by a plastical working of the material. The implant is fixed by being covered with surrounding soft tissue which is closed by suturing.

The major advantage of the present invention is that the handling of the substitute material is considerably facilitated and that particles thereof are prevented from escaping from the application site. If this would happen, the particles could cause irritation or complication at other places of the body.

Another advantage is that the mixture can be sterilized and stored in closed packages without any changes of properties.

The invention will now be described with reference to the accompanying drawings, which show non-limiting embodiments of the invention only and wherein

FIG. 1 is a phase diagram of a monolein-water mixture; and

FIG. 2 is a diagrammatic plan view of a skull portion with an implant product therein.

An ideal monoglyceride for use in the implant material according to the present invention is oleic acid, since monoglycerides with a higher degree of unsaturation are more easily oxidated which might cause risks of the formation of toxic substances. Reference is made to the diagram shown in figure 1, which is a phase diagram for a mixture of monoolein and water indicating the relationship between temperature and water content related to the existence of the phase wherein the monoolein-water mixture is liquid and the phase wherein the monoolein-water mixture has a gel-like structure with high viscosity. If the water phase contains salts of physiological concentration or proteins from the blood or lymph system, the diagram will not be changed. Thus, starting from monoolein having a water content of about 4% (weight by weight), the phase is liquid in the temperature range from about 20 to 40°C, i.e. below the body temperature (about 36°C). This phase is indicated as L2 because the water molecules thereof form a reversed micellular structure. After swelling in contact with

water or an aqueous liquid, such as blood or the humidity of soft tissue, the viscous phase D (D stands for diamond glitter which is the water canal structure of the phase) will be obtained, which is a cubic liquid crystalline phase.

An implant material of the D-phase of monoolein in soft tissue and in bone tissue has been found to be perfectly biocompatible therewith and to cause no changes of inflammatory characters. Probably this is due to the fact that monoolein is present in the body and will be exchanged with esterases (lipases) in the normal lipid metabolism. Another favorable factor probably is that the cubic structure is identical with the lipid structure of biological membranes, i.e. a biomolecular layer with the polar group facing outwardly towards the water medium.

In order to obtain the liquid phase at room temperature, the water content of the monoolein-water mixture should be within the range of from about 3,5 to 4% (weight by weight). At higher water contents a lamellar liquid crystal phase will be formed, and this has been found useful since the viscosity thereof is low. However, use of the liquid L2-phase is preferred since this phase provides ideal consistency conditions for the implant material.

EXAMPLE 1

Monoolein is heated to a temperature just above the melting point thereof (36°C), preferably to 40°C. When the monoolein is completely melted, a physiological saline solution of the same temperature (40°C) is added so as to obtain a weight ratio of monoolein/water from 97:3 to 85:15 and preferably 96,2:3,8. The resulting L2-phase is allowed to cool to room temperature and then granules of calcium hydroxyapatite, APACERAM®, are added, with stirring, said addition being made to a volume ratio of calcium hydroxyapatite/L2-solution of 3:1.

The implant material thus obtained has a toothpaste-like consistency and can be stored in closed packages, e.g. a one-way syringe, at a temperature ranging from about 0°C to 40°C without any changes of properties. When the material is to be used, a temperature within the range of from 20°C to 35°C should be imparted thereto. In this context it should be noted that a rise of temperature will mean a lowering of the viscosity.

In figure 2 there is shown a plate 10 obtained from a block of calcium hydroxyapatite which plate is located and suitably fixed in an opening 11 of a scull portion 12. The implant material can be applied to the plate and the surrounding region of the scull indicated by hatching at 13 by dispensing the low viscosity implant material from a syringe wherein it has been stored, and the material is then smeared out at least in the region 13. When the material is contacted with the scull, the viscosity thereof may decrease due to a temperature rise, but when the material then comes into contact with any body fluid, such as blood, the viscosity thereof will increase in a few seconds so as to form a well confined mass of high

viscosity which can still be plastically worked at the site of application so as to impart to the material the desired shape and to provide a smooth and tight transition between the plate and the surrounding bone of the scull, whereby inaccuracies between the plate 10 and the edges of the opening 11 due to difficulties to accurately work the hard and brittle calcium hydroxyapatite blocks to the exact form of the opening are equalized by means of the applied implant material.

The applied implant material is fixed in the intended position by covering the scull and the implant region by means of surrounding soft tissue which is then closed by suturing.

EXAMPLE 2

As in example 1 monoolein is heated just over the melting point thereof (36°). A vegetable oil, such as soybean oil (or another triglyceride oil), is added to the melted monoolein so as to obtain a weight ratio of 80-90% monoolein and 2-12% soybean oil. Then, 3-5% of a physiological saline solution is added thereto, so as to obtain a weight ratio of monoolein/soybean oil/water of 85:10:5. After cooling of the resulting L2-phase to room temperature, granules of calcium hydroxyapatite are added thereto as in example 1 to a ratio of calcium hydroxyapatite /L2-solution of 1:1-5:1 by volume. The mixture thus obtained will have a lower viscosity than the mixture obtained in example 1, and the viscosity thereof will be further reduced if adding more soybean oil. The material will behave in a manner similar to that of the material described in example 1 when applied to bone in a human or animal body.

Claims:

1. An implant material for restoring bone tissue, comprising a particulate biocompatible non-organic bone tissue substitute and a mixture of an aqueous liquid and a monoglyceride, which material remains in the liquid phase below a predetermined temperature.

2. An implant material according to claim 1, wherein the bone tissue substitute is selected from the group consisting of calcium hydroxyapatite, alumina, tricalcium phosphate and calcium aluminate.

3. An implant material according to claim 1, wherein the bone tissue substitute comprises a mineral.

4. An implant material according to claim 1, wherein the bone tissue substitute comprises titanium.

5. An implant material according to claim 1, wherein the bone tissue substitute comprises calcium hydroxyapatite.

6. An implant material according to claim 5, wherein the monoglyceride comprises an unsaturated fatty acid.

7. An implant material according to claim 6, wherein said unsaturated fatty acid is monoolein.

8. An implant material according to claim 7, wherein the weight ratio of monoolein to water is within the range of about 97:3-85:15.

9. An implant material according to claim 7, wherein the volume ratio of calcium hydroxyapatite to a mixture of an aqueous liquid and monoolein is 3:1.

10. An implant material according to claim 7, wherein a vegetable oil is added to the monoolein.

11. An implant material according to claim 10, wherein said oil is a triglyceride oil.

12. An implant material according to claim 11, wherein the ratio of monoolein, triglyceride oil and aqueous liquid is 85:10:5.

13. An implant material according to claim 1, wherein said temperature is about 40°C.

14. A method of preparing an implant material for restoring bone tissue, comprising the measures of mixing a particulate biocompatible non-organic bone tissue substitute and a mixture of an aqueous liquid and a monoglyceride, which material remains in the liquid phase below a predetermined temperature.

15. A method according to claim 14, wherein the monoglyceride comprises an unsaturated fatty acid.

16. A method according to claim 15, wherein said unsaturated fatty acid is monoolein.

17. A method according to claim 16, wherein said monoolein is melted before adding the aqueous liquid thereto.

18. A method according to claim 17, wherein an oil is added to the melted monoolein.

19. A method according to claim 18, wherein the amount of monoolein is within the range of from about 80 to about 90 percent by weight and the amount of oil within the range of from about 2 to about 12 percent by weight.

Abstract:

An implant material for restoring bone tissue in human or animal body has been produced. Said material comprises a particulate biocompatible non-organic bone tissue substitute, an aqueous liquid and a monoglyceride. Below a predetermined temperature, the composition is a mass of low viscosity which is easy to apply to a bone cavity or a bone with an implant body. The viscosity of the implant material increases due to the formation of a cubic liquid crystalline phase when the material is contacted with a body fluid or another liquid present on or supplied to the site of application.

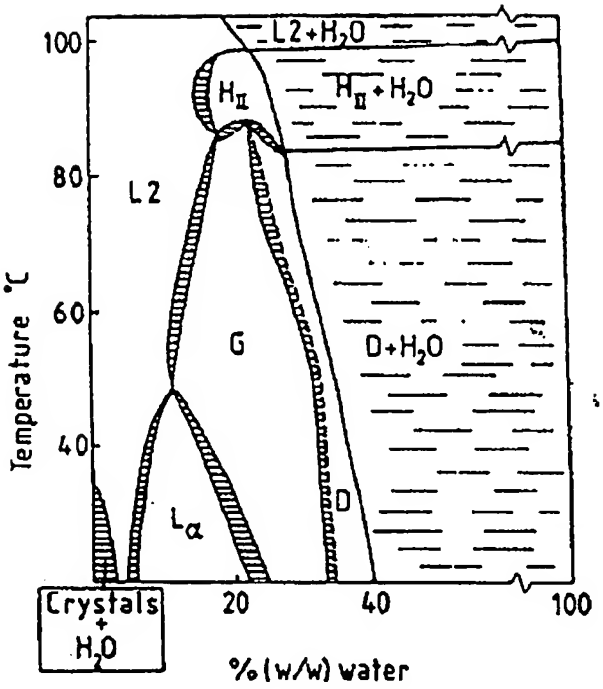

Fig. 1

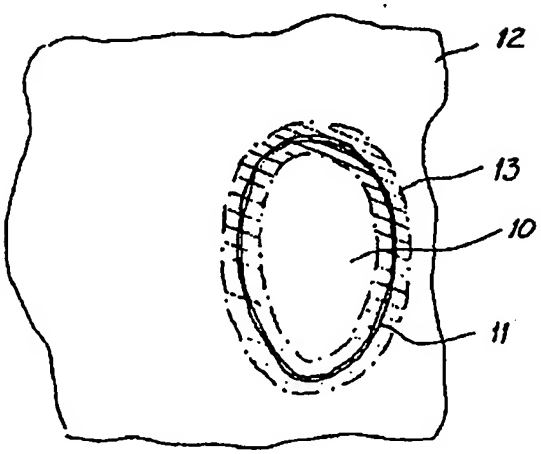

Fig. 2

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